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The effect of theta burst stimulation (TBS) on aphasia in stroke patients: a protocol of systematic review and meta-analysis

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Abstract

Background Prior studies have 3suggested that theta burst stimulation (TBS) may be a promising intervention for the rehabilitation of aphasia after stroke. However, the results of these investigations have been inconsistent, with no definitive consensus on its efficacy and safety. Given the inconclusive nature of the existing evidence, this study aims to conduct a comprehensive and systematic review to evaluate the therapeutic effects of TBS on aphasia in stroke patients.

Methods We will perform an extensive search of eight online databases from their inception to August 1, 2024, to identify relevant randomized controlled trials (RCTs) that examine the impact of TBS on aphasia in stroke patients. The primary outcome will be the severity of aphasia, assessed using a suite of standardized evaluation tools. Secondary outcomes will include measures of naming, repetition, comprehension, spontaneous speech, aphasia quotient, quality of life, and documentation of adverse events. The review process will involve rigorous study selection, data extraction, risk of bias assessment, and evaluation of the certainty of evidence by two independent reviewers. Data synthesis and statistical analysis will be conducted using Review Manager (RevMan) software, version 5.3. If significant heterogeneity is not detected among the studies, a meta-analysis will be performed. Otherwise, a narrative qualitative summary will be provided. The quality of evidence will be assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system.

Discussion This study will be the first systematic review to comprehensively synthesize the existing evidence regarding the application of TBS in the treatment of aphasia in stroke patients. The findings are expected to provide valuable insights for clinicians and policymakers, facilitating the development of more equitable and high-quality healthcare services for this patient population.

Systematic review registration PROSPERO CRD42024521347.

Keywords Theta burst stimulation, Aphasia, Stroke, Systematic review, Meta-analysis

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Background

Description of the condition

Aphasia, characterized by an acquired disruption in language production and comprehension, is a significant and prevalent consequence of stroke [1], primarily resulting from damage to the left cerebral hemisphere [2]. The Global Burden of Disease 2017 study [3] revealed that approximately 21% to 38% of stroke survivors experience post-stroke aphasia [4]. This condition affects multiple aspects of communication, including speaking, listening, reading comprehension, writing, and everyday conversation. Up to 61% of stroke survivors continue to experience language deficits 1 year after the onset of stroke [5, 6]. These speech impairments can significantly impede functional recovery, diminish communication abilities, and disrupt the performance of routine daily activities [7]. Additionally, aphasia is associated with an increased risk of depression and higher mortality rates [8], prolonged hospital stays [9], and reduced likelihood of successful return to employment. Despite these substantial implications, there is a paucity of well-developed management strategies specifically aimed at aphasia. There is a critical need for evidence to elucidate the impact of interventions on language recovery following a stroke.

Description of the intervention

Adherence to clinical practice guidelines is crucial for delivering high-quality care and improving the prognosis of patients with post-stroke aphasia. However, there is a notable lack of high-quality, specific clinical guidelines for managing post-stroke aphasia [10]. Emerging evidence supports the significant benefits of speech and language therapy in enhancing the communicative abilities of individuals with aphasia [11]. Unfortunately, this therapeutic approach requires more comprehensive clinical guidance to ensure the delivery of high-quality treatment [10]. The cost of treatment can be substantial, with progress often gradual and outcomes sometimes limited [12]. In light of these challenges, researchers have explored alternative methods. Encouragingly, repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, has demonstrated potential in the rehabilitation of post-stroke aphasia in recent years [13, 14]. Theta burst stimulation (TBS), an innovative variant of rTMS, has been shown to elicit more pronounced and enduring effects than traditional rTMS protocols within a shorter period of continuous stimulation [15, 16]. Notably, intermittent theta burst stimulation (iTBS) has been found to particularly enhance auditory comprehension and language recovery in patients with chronic post-stroke aphasia, offering advantages over low-frequency rTMS (LF-rTMS) [17]. Collectively, these findings suggest that TBS may be a preferable alternative to conventional rTMS for facilitating stroke rehabilitation [18].

How the intervention might work

Neuroplasticity, the brain's ability to reorganize and adapt, is a fundamental mechanism in stroke recovery, allowing for the redistribution of functions from damaged to intact regions [19]. Transcranial magnetic stimulation (TMS) leverages the principle of electromagnetic induction, utilizing rapidly changing magnetic pulses to stimulate neuronal activity in the targeted cerebral cortex. This stimulation modulates cortical excitability and prompts neural network reorganization, which is essential for functional recovery [18–20]. Recent evidence [21, 22] suggests that improvements in aphasia are closely associated with the reorganization of the functional balance between the compromised perilesional ipsilateral hemisphere and the intact contralateral hemisphere. Specifically, a stroke in the left hemisphere can disrupt the normal inhibitory interhemispheric connections, leading to relative hyperactivity in the right hemisphere [23]. This overactivation can, in turn, excessively inhibit the functionality of preserved areas within the left hemisphere, thereby impeding language recovery [24]. To address these neuroplasticity models, researchers have applied excitatory rTMS to the affected regions in the left hemisphere [25] and inhibitory rTMS to corresponding areas in the right hemisphere [26, 27]. Neuroimaging studies [28, 29] have theorized that spared regions in the compromised left hemisphere may assume the functions of the damaged cortex following rTMS stimulation, with the reactivation of these areas correlating with optimal recovery. Theta Burst Stimulation (TBS), an advanced variant of rTMS, has been developed to closely replicate the brain's natural firing patterns, allowing for the precise modulation of excitability in specific cortical areas [18, 30]. TBS has gained considerable attention as a therapeutic intervention in stroke rehabilitation, often based on the interhemispheric inhibition hypothesis [31]. The hypothesis posits that TBS can recalibrate the disrupted inhibitory balance between hemispheres, thereby facilitating recovery [18]. In summary, TBS represents a promising approach to enhancing neuroplasticity and promoting functional recovery in patients with post-stroke aphasia by modulating cortical excitability and reorganizing neural networks.

Why it is important to do this review

To date, TBS has shown clear benefits over traditional rTMS protocols, primarily due to its lower intensity, shorter application duration, and long-lasting effects [15, 16]. A recent randomized controlled trial (RCT) has further demonstrated that iTBS is superior to LF-rTMS

in improving auditory comprehension [17]. Despite an increasing number of studies on TBS interventions for post-stroke aphasia [17, 25, 32–36], conclusive evidence regarding its efficacy in aphasia recovery is still lacking. This systematic review aims to provide the first comprehensive synthesis of the existing evidence on TBS as a therapeutic option for post-stroke aphasia. Our objective is to synthesize the current knowledge of TBS's role in treating post-stroke aphasia and to outline potential strategies for clinical application and future research aimed at utilizing TBS to enhance rehabilitation in this patient population.

Methods

This systematic review will adhere to the rigorous standards outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Systematic Review protocols (PRISMA-P) [37]. Our dedication to transparency and protocol adherence is further demonstrated by the registration of this review protocol in the International Prospective Register of Systematic Reviews (PROSPERO), under the registration number CRD42024521347. This registration ensures that our methodology and findings are subject to rigorous scrutiny and are accessible for the broader scientific community, thereby enhancing the credibility and impact of our research.

Criteria for considering studies for this review

Types of studies

This systematic review will include RCTs that compare TBS with low-frequency rTMS (LF-rTMS), a sham control group, or other therapeutic interventions for aphasia in stroke patients. To ensure a comprehensive and inclusive synthesis of the available evidence, no limitations will be imposed on the language of the studies, their publication status, or the date of publication. However, to maintain the rigor of the comparative analysis, crossover trials and quasi-randomized controlled trials will be excluded from this review.

Types of participants

Eligibility for inclusion in this review will be extended to patients who meet the established diagnostic criteria for post-stroke aphasia. This review will adopt an inclusive approach, enrolling all eligible subjects regardless of gender, age, ethnicity, stroke classification, or the chronicity of their aphasia. This broad criterion will facilitate a comprehensive analysis that is representative of the diverse patient population affected by this condition.

Types of interventions

The interventions considered in this review will include TBS administered either as a standalone treatment or in conjunction with conventional rehabilitation. TBS encompasses both continuous Theta burst stimulation (cTBS) and iTBS, thereby ensuring a comprehensive evaluation of the spectrum of TBS applications in the context of post-stroke aphasia rehabilitation.

Types of comparators

The following comparator groups will be considered:

1. TBS versus LF-rTMS.
2. TBS versus routine care.
3. TBS versus sham stimulation.
4. TBS in conjunction with conventional rehabilitation versus conventional rehabilitation alone.

Trials that exclusively compare different stimulation localizations of TBS shall be excluded.

Types of outcome measures

Primary outcome Aphasia severity was assessed by the following scale:

1. BDAE: Boston diagnostic aphasia examination。
2. ABC: aphasia battery of Chinese.
3. AAT: Aachen aphasia test.
4. CCAT: concise China aphasia test scale.
5. WAB: western aphasia battery.
6. CPNT: computerized picture naming test.

Secondary outcomes

The secondary outcomes will encompass naming ability, repetition accuracy, comprehension, spontaneous speech, aphasia quotient, quality of life, other relevant outcomes, and adverse events.

Search methods for identification of studies

Electronic searches

The following electronic databases will be systematically searched for published RCTs from inception until 1 August 2024: PubMed, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials, Chinese Biomedical Databases, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Wan Fang Digital Journals. No language

restrictions will be applied. The following medical search headings (MeSH) and keywords will be used: aphasia, hemorrhagic stroke, ischemic stroke, stroke, transcranial magnetic stimulation, randomized controlled trial, and controlled clinical trial. Search strategies for each database will be tailored in accordance with the Cochrane Handbook for Systematic Reviews and Meta-Analyses. The search strategy for EMBASE is detailed in Table 1.

Searching other resources

Completed or ongoing trials will be identified from the following clinical trial registries: the NIH Clinical Registry ClinicalTrials.gov (https://www.ClinicalTrials.gov/) and the Chinese Clinical Registry (http://www.chictr.org/en/). These registries provide comprehensive information on clinical trials, which will be used to identify relevant studies that may not have been indexed in the primary databases searched.

Data collection and analysis

Selection of studies

Two independent reviewers (YT and XR-W) will import the search results into EndNote X8 and rigorously evaluate the eligibility of identified studies against our predefined inclusion criteria. In the initial phase of study selection, reviewers will screen titles and abstracts to rapidly exclude any clearly irrelevant publications. For citations deemed potentially eligible, full texts will be obtained, and any duplicate reports of the same study will be consolidated for comprehensive evaluation against our eligibility criteria. If necessary, direct correspondence with study investigators will be initiated to resolve any ambiguities regarding study eligibility. Reviewers will collaboratively reach a final decision on the inclusion of studies and cross-verify their selection outcomes. In the event of disagreements, consensus will be sought through discussion. If disputes persist, a third reviewer (HJ-F) will act as an arbitrator. Studies that do not meet the inclusion criteria will be archived in a designated folder within EndNote X8, and the rationale for their exclusion will be meticulously documented in an Excel spreadsheet. To quantitatively assess the level of agreement between the two primary reviewers during the inclusion/exclusion decision-making process, we will calculate a kappa statistic (as per the guidelines outlined in the Cochrane Handbook). Each study selected for inclusion will be assigned a unique study ID, formatted as follows: the surname of the first author, followed by the year of publication. The entire selection process will be graphically summarized in a PRISMA flowchart (Fig. 1), providing a transparent and detailed depiction of our systematic review methodology.

Data extraction and management

To ensure the rigor and accuracy of our data extraction process, two independent reviewers (WQ-Z and YQ-G) will undergo a comprehensive training program and achieve proficiency with our pre-established data collection instrument. Any disagreements will be resolved through discussion between the two reviewers, with arbitration by a third reviewer (GC-Z) if necessary. This

Table 1 Search strategy in Embase

#1	'randomized controlled trial'/exp
#2	'controlled clinical trial'/exp OR 'clinical trial'/exp OR 'clinical study'/exp
#3	randomized:ab,ti OR placebo:ab,ti OR randomly:ab,ti OR trial:ab,ti
#4	'controlled clinical trial':ab,ti OR 'randomized controlled trial':ab,ti
#5	#1 OR #2 OR #3 OR #4
#6	'aphasia'/exp OR 'language disability'/exp OR 'communication disorder'/exp OR 'speech disorder'/exp
#7	aphasia:ab,ti OR 'language disability':ab,ti OR 'communication disorder':ab,ti OR 'speech disorder':ab,ti
#8	#6 OR #7
#9	'cerebrovascular accident'/exp OR 'ischemic stroke'/exp OR 'brain hemorrhage'/exp OR 'brain ischemia'/exp OR 'cardioembolic stroke'/exp
#10	'cerebrovascular accident':ab,ti OR 'ischemic stroke':ab,ti OR 'brain hemorrhage':ab,ti OR 'brain ischemia':ab,ti OR 'cardioembolic stroke':ab,ti OR stroke:ab,ti
#11	#9 OR #10
#12	#8 AND #11
#13	'transcranial magnetic stimulation'/exp OR 'repetitive transcranial magnetic stimulation'/exp OR 'magnetic stimulation'/exp
#14	'transcranial magnetic stimulation':ab,ti OR 'repetitive transcranial magnetic stimulation':ab,ti OR 'magnetic stimulation':ab,ti OR 'theta burst stimulation':ab,ti
#15	#13 OR #14
#16	#5 AND #12 AND #15

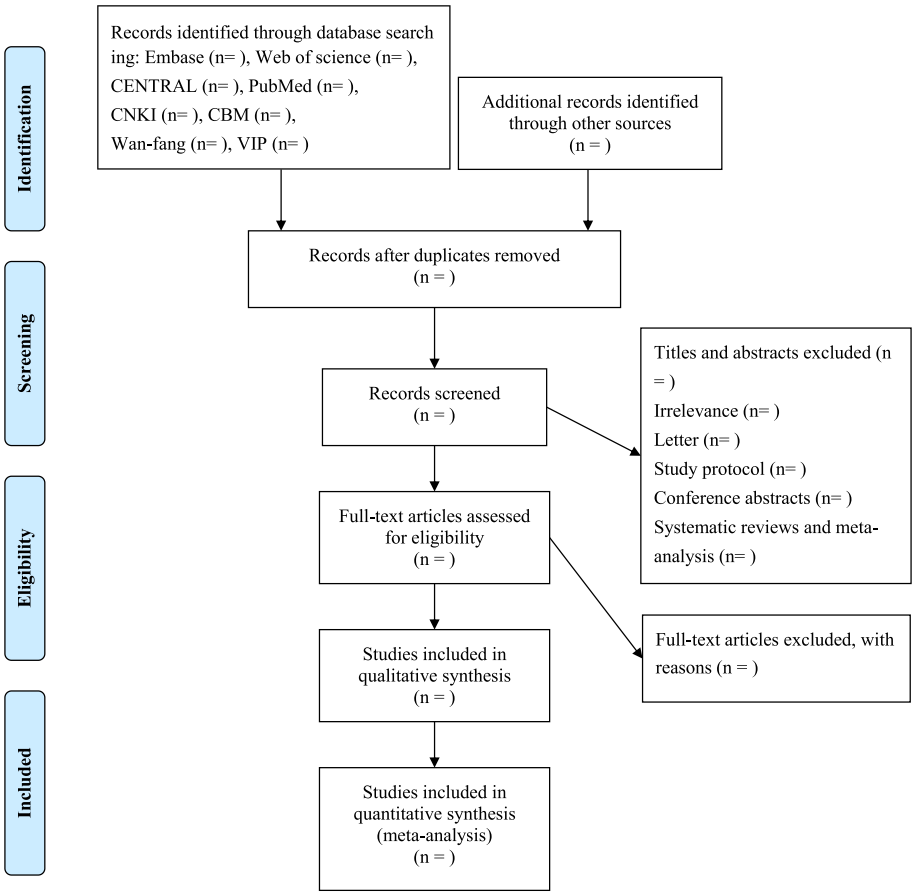

Fig. 1 Flow chart of the study

instrument, meticulously designed, will encompass the following eight critical elements:

1. Source: Study ID, title, first author's name and affiliation, source of publication, year of publication, citation, and contact details.

2. Eligibility: confirmation of eligibility for review, reasons for exclusion.

3. Methods: study design, total study duration, sequence generation, allocation sequence concealment, blinding, and other concerns about bias.

4. Participants: total number, study setting, diagnostic criteria, age, sex, country, and co-morbidity.

5. Interventions: total number of intervention groups, specific interventions for each group intervention details, integrity of intervention.

6. Outcomes: outcomes and time points, outcome definition, units of measurement, and scales (upper and lower limits, and whether the high or low score is favorable).

7. Results: number of participants allocated to each intervention group, summary data for each outcome of interest (sample size, missing participants, summary data for each intervention group, subgroup analyses, effect estimate with confidence interval, and *P* value).

8. Miscellaneous: funding source, key conclusions of the study authors, miscellaneous comments from the study authors, references to other relevant studies, correspondence required, and miscellaneous comments by the review authors.

Assessment of risk of bias in included studies

Reviewers CH and LH-Z will independently utilize the refined Risk of Bias in Randomized Trials (RoB 2) tool (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials) to systematically evaluate the risk of bias across specific domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. The RoB 2 tool employs response options of "yes", "probably yes", "probably no", "no", and "no information" to guide the overall judgment of bias risk as "low risk", "some concerns", or "high risk" [38]. The reviewers'

ratings will be cross-verified, and any discrepancies will be resolved through discussion. If consensus cannot be reached, a third reviewer (SH-Z) will provide arbitration as necessary.

Measures of treatment effect

The efficacy of treatments will be rigorously measured and subjected to statistical analysis using the Review Manager (RevMan) software, version 5.3. For binary outcomes, the risk ratio along with 95% confidence intervals (CIs) will be calculated. For continuous outcomes, the mean difference (MD) will be used in the meta-analysis if all RCTs have employed identical scales for outcome measurement. If RCTs assess the same outcome with diverse measurement methods, the standardized mean difference (SMD) will be utilized as the metric for the meta-analysis.

Unit of analysis issues

We will include RCTs with a simple parallel group design. In these studies, participants are randomly assigned on an individual basis to one of two intervention groups. For each outcome, a singular measurement is collected and analyzed from each participant. It is also possible that the same outcome may be subject to multiple observations.

Dealing with missing data

In cases where data are incomplete, we will proactively contact the original investigators to obtain the missing information. Additionally, sensitivity analyses will be performed to assess the robustness of our findings to plausible variations in the underlying assumptions. The results of these analyses will be essential for interpreting the overall findings. The potential impact of missing data on the validity of our conclusions will be thoroughly deliberated within the Discussion section, ensuring that our inferences are well-grounded and transparent to the reader.

Assessment of heterogeneity

The chi-squared (χ^2) test, as illustrated in the forest plots of Cochrane reviews, is a statistical measure to assess heterogeneity among study results. In line with the Cochrane Handbook guidelines, a P value less than 0.10 is considered to indicate statistical significance. The interpretation of the I^2statistic, which quantifies the proportion of total variation across studies due to heterogeneity, is typically guided by the following thresholds: values from 0 to 40% may suggest minimal heterogeneity; those from 30 to 60% could indicate moderate heterogeneity; figures between 50 and 90% may point to substantial heterogeneity; and values within the range of 75 to 100% signify considerable heterogeneity.

Assessment of reporting biases

As a general guideline, funnel plot asymmetry assessments are typically performed when a meta-analysis includes at least 10 studies. A visual inspection of the funnel plot will be conducted to identify any evidence of reporting bias within the meta-analysis. In the absence of bias, the distribution of study results in the funnel plot should ideally exhibit approximate symmetry, forming an inverted funnel shape.

Data synthesis

Data synthesis will be performed using the Review Manager (RevMan) software, version 5.3. RevMan provides two primary analytical methods for meta-analysis: the fixed-effect model and the random-effects model. The choice of the analytical method for data synthesis and analysis will be based on the degree of statistical heterogeneity observed in the dataset. In the absence of heterogeneity, both methods are expected to yield similar results. However, in the presence of heterogeneity, the random-effects model typically produces wider confidence intervals for the effect size and correspondingly less significant P values. Therefore, the principles guiding data analysis in this study are as follows:

1. A fixed-effects model will be used when statistical heterogeneity is minimal or absent.
2. If significant heterogeneity is detected but does not exceed 50%, a random-effects model analysis will be conducted.
3. In cases where substantial and unexplained heterogeneity is identified among the trials, meta-analysis will be omitted. Instead, efforts will be directed toward identifying potential sources of heterogeneity from both clinical and methodological perspectives, followed by a narrative qualitative summary.

Subgroup analysis and investigation of heterogeneity

If heterogeneity is identified among a cohort of trials deemed appropriate for meta-analysis, the following methodical steps will be meticulously executed:

1. The accuracy of the data will be rigorously re-evaluated by the reviewers to ensure the integrity of the analysis.
2. An in-depth exploration of the heterogeneity will be undertaken through the execution of subgroup analyses or meta-regression, where feasible. Provided that adequate data are available, these analyses will be stratified by stroke type, the chronicity and severity

of post-stroke aphasia, and the age demographic of the participants.
3. A random-effects meta-analysis model will be chosen to accommodate the variability in study outcomes, thereby acknowledging the presence of heterogeneity.
4. If the dataset includes outlier studies with discordant results in comparison to the collective findings, sensitivity analyses will be systematically conducted to assess the robustness of the overall meta-analytic conclusions.

Sensitivity analysis

Sensitivity analyses are essential replicates of the meta-analytic process, designed to evaluate the robustness of the primary decisions made during the review. When the inclusion of certain trials is uncertain due to incomplete reporting (e.g., those with small sample sizes, methodological flaws, or missing data), the sensitivity will be conducted in two stages: first including all identified studies, and then, excluding studies that do not meet the eligibility criteria. The results of the sensitivity analysis will be presented concisely in a summary table to ensure transparency and facilitate comparison. Additionally, the implications of the risk of bias, as indicated by the sensitivity analysis findings, will be thoroughly discussed in the "Discussion" section of our review.

GRADE assessment

The certainty of the evidence will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [39]. This systematic approach assigns one of four grades—'high', 'moderate', 'low' or 'very low'—to each outcome, considering limitations in the design and implementation, indirectness of evidence, unexplained heterogeneity, imprecision of results, and high probability of reporting bias [40]. Two independent reviewers(CH and LH-Z) will utilize the "GRADEprofiler" software to assess the evidence and then import the findings into the Review Manager (RevMan) version 5.3. In case of discrepancies between the reviewers' assessments, a third reviewer (SH-Z) will arbitrate. A comprehensive "Summary of Findings" table, derived from the GRADE evaluation, will be compiled and included in the final report to summarize the key outcomes of the review.

Discussion

Mechanism of TBS in the rehabilitation of aphasia after stroke

TBS has emerged as a promising modality within the rTMS paradigm for stroke rehabilitation, demonstrating more pronounced and enduring neurophysiological responses compared to traditional rTMS protocols, particularly within a condensed stimulation timeframe [41]. The main difference from traditional rTMS is that TBS can induce changes in cortical excitability with a short duration of stimulation (40–190 s), and these changes can last for at least 20–30 min after the stimulation ends. The therapeutic efficacy of TBS is attributed to its multifaceted mechanisms. From the perspective of synaptic plasticity, TBS can enhance brain plasticity by modulating synaptic transmission, which manifests as long-term potentiation (LTP) and long-term depression (LTD). TBS regulates the activity of neurotransmitter receptors, alters the concentration of postsynaptic calcium ions, and influences the postsynaptic responses mediated by neurotransmitter receptors, thereby promoting the recovery of brain nerve function and affecting language functional areas in remote regions [42]. At the gene and protein level, TBS influences gene expression and protein synthesis, thereby altering synaptic remodeling. TBS can regulate the expression of various gene proteins through different mechanisms, affecting the activity of different types of inhibitory cells and ultimately promoting brain function recovery after injury [43].

Application of TBS in the rehabilitation of aphasia after stroke

Compared to traditional rTMS, TBS offers unique advantages such as shorter stimulation duration, lower stimulation intensity, and fewer pulse numbers, making it a highly promising NIBS technique [44]. Currently, the application of TBS in aphasia treatment methods is still in a relatively nascent stage. Fortunately, new RCTs have been disseminated across both Chinese [45] and English electronic databases [34]. Observed iTBS-induced language improvements and associations between delayed fMRI changes and aphasia improvements support the therapeutic and neurorehabilitative potential of iTBS in post-stroke aphasia recovery [33]. cTBS of the right pSTG may improve language production by suppressing intrinsic activity of the right fronto-thalamic-cerebellar circuit and enhancing the involvement of the right temporoparietal region [46]. This is anticipated to significantly aid in the formulation of definitive conclusions regarding the efficacy of TBS in the rehabilitation of aphasia following stroke. In the forthcoming research, we intend to augment and extend our search parameters within Chinese databases to encompass a more exhaustive collection of relevant RCTs, thereby enhancing the comprehensiveness of our study. This systematic synthesis is poised to deliver significant insights, elucidating the therapeutic potential of TBS within the expansive framework of rehabilitation strategies for post-stroke aphasia.

Future directions and limitations

Future research should prioritize large-scale, high-quality, multicenter studies to further elucidate the mechanisms of TBS and explore the optimal treatment protocols. Additionally, future studies should investigate the synergistic effects of TBS with other advanced rehabilitation modalities, such as robotics, gamified rehabilitation, and virtual reality, to provide comprehensive rehabilitation strategies for post-stroke aphasia patients. This study acknowledges certain limitations. The scope of our literature search was confined to publications in Chinese and English, which may have introduced a bias in the selection of studies and influenced the synthesis of findings. Additionally, the variability in inclusion criteria, definitions of exposure, and reported outcomes across the included studies could have affected the comparability of results. Furthermore, the heterogeneity observed among the studies may have precluded the presentation of findings in a meta-analytic format, limiting the ability to draw more definitive conclusions from the aggregated data.

Abbreviations

GRADE	Grading of Recommendations Assessment, Development, and Evaluation
rTMS	Repetitive transcranial magnetic stimulation
TBS	Theta burst stimulation
iTBS	Intermittent theta burst stimulation
LF-rTMS	Low-frequency rTMS
TMS	Transcranial magnetic stimulation
RCT	Randomized controlled trial
PRISMA-A	Preferred Reporting Items for Systematic Reviews and Meta-Analyses for systematic review protocols
cTBS	Continuous theta burst stimulation
MeSH	Medical Search Headings
CIs	Confidence intervals
MD	Mean difference
SMD	Standardized mean difference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-02823-1.

Additional file 1.

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Not applicable.

Authors' contributions

HJ-F conceived the review protocol and drafted the manuscript. JL revised the study design. HJ-F, YT, and XR-W formed the data synthesis and analysis plan. GC-Z, WQ-Z, and YQ-G participated in the design of the search strategy and data extraction data set. SH-Z, CH, and LH-Z formed the data synthesis and analysis plan. In practice, JL and GC-Z will monitor each procedure of the review and are responsible for quality control. All authors have read and approved the publication of the protocol.

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Data availability

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable. Ethical approval is waived for this study as it does not involve the use of private patient data.

Consent for publication

The findings are slated for publication in peer-reviewed journals.

Competing interests

The authors declare that they have no competing interests.

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